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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/051,013 10/09/98 BESTOR T 48075-B-PCT

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EXAMINER

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ART UNIT	PAPER NUMBER
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1633

10

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Commissioner of Patents and Trademarks**

<b>Office Action Summary</b>	Application No. <b>09/051,013</b>	Applicant(s) <b>T.H. Bestor</b>
	Examiner <b>Janet M. Kerr</b>	Group Art Unit <b>1633</b>

Responsive to communication(s) filed on Jan 16, 2001

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

Claim(s) 1-47 is/are pending in the application.

Of the above, claim(s) 2, 3, 5, 13, 14, 17-23, 29, 34-41, and 47 is/are withdrawn from consideration.

Claim(s) \_\_\_\_\_ is/are allowed.

Claim(s) 1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46 is/are rejected.

Claim(s) \_\_\_\_\_ is/are objected to.

Claims \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All  Some\*  None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 9

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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***Response to Amendment***

Applicant's amendment, filed 1/16/01, has been entered.

Claims 1-47 remain pending.

Claims 2, 3, 5, 13, 14, 17-23, 29, 34-41, and 47 had been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

Claims 1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46 are being examined on the merits.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record and the reasons below.

The claims are directed to a chimeric protein which comprises a zinc three-finger DNA binding polypeptide linked to a CpG-specific DNA methyltransferase polypeptide, wherein the DNA binding polypeptide binds sufficiently close to a promoter sequence of a target gene, wherein the target gene is an endogenous gene associated with cancer, wherein the promoter

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sequence contains a methylation site, and wherein the site is specifically methylated such that activity of the promoter, and thus, expression of the target gene is inhibited; vectors comprising a polynucleotide encoding the chimeric protein, cells containing the vector, and pharmaceutical compositions containing the vector. As stated in the previous office action, the specification does not disclose a chimeric peptide which specifically targets a promoter of an endogenous gene associated with cancer. While the specification discloses that target genes include the cancer related genes collagenase 92 KD Type 4, collagenase 72 KD Type 4, osteopontin, calcyclin, fibroblast growth factor, epidermal growth factor, matrilysin and stromolysin, the specification does not disclose the sequence (amino acid or polynucleotide) required in the zinc three finger binding polypeptide which will allow such targeting specificity such that methylation of the promoter occurs and results in inhibition of expression of the endogenous gene. Furthermore, the specification does not provide any polynucleotide sequences which encode the chimeric proteins of the elected invention.

Applicant's arguments filed 1/16/01 have been fully considered but they are not persuasive. It is argued that the written description standard is an objective test for the sufficiency of support in a parent application and whether the disclosure reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter, citing *In Re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983). It is argued that at the time of applicant's effective filing date, one of skill in the art would have known of many promoter sequences of genes known to be involved in cancer. Applicants provide Exhibit O to support this argument. Exhibit O is a listing of 12 GenBank Accession numbers, all of which represent sequences of osteopontin (see pages 8-9 of applicant's Response). It should be noted that the sequences applicant refers to as GenBank Accession numbers, 734345, 673889, 211276, 654575, 189404, 200157, 205867, 205859, 200159, 162890, 189150, and 273962 are cited as mRNAs, cDNAs, or ESTs, i.e., these sequences do not encompass promoter regions. Similarly, the sequence applicant refers to as GenBank Accession number 424135, is an intronic sequence, not a promoter sequence. Thus,

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these sequences are not relevant. Although two of the listed sequences, 164599 and 404635, comprise the promoter regions of the pig and chicken osteopontin promoters, there is no teaching in these citations of the promoter sequences in which the DNA binding protein of the chimeric protein of the instant invention binds sufficiently close to said promoter sequence, and wherein said promoter sequence contains a methylation site, and further wherein the chimeric protein specifically methylates the site and inhibits activity of the promoter and thus inhibits expression of the osteopontin gene.

Applicant also argues that various DNA binding proteins were known in the art to specifically bind to specific DNA binding sequences involved in cancer. It is asserted that DNA binding proteins which bind to promoter sequences found in the promoters of cancer-related genes were also well known (see page 9 of applicant's Response). Applicant provides examples of the DNA binding proteins, MDBP and MIBP1, which bind to specific sites in the first intron of human c-myc gene or the rat c-myc gene, respectively. Again, these are introns and not promoter regions. With respect to the reference teaching the DNA-binding protein MSSP-2, there is no indication that this binding protein binds sufficiently close to a promoter sequence which contains a methylation site. Contrary to applicant's assertions, the prior art does not provide the chemical and structural features of the claim-designated DNA binding protein components necessary for the claimed invention.

It is argued that one of skill in the art would have known to recognize a methylation site in a promoter sequence in view of the disclosure in the instant application, and further in view of the reviews by Bestor and Meehan *et al.* (see applicants' Response, page 10). Applicant refers to the figure legends for Figure 1, 2, and 3 on page 5 of the specification, and the figure legend for Figure 8 on page 7. These arguments are not persuasive as the legends in the specification do not disclose the structural features of the elected invention. The legends for Figures 1 and 2 disclose the distribution of CpG sites and transcription factor binding sites in the 5' LTR of HIV-1, and the sequence of HIV-1 5' LTR. HIV-1 is not an endogenous gene associated with cancer. The

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legend for Figure 3 discloses a generic teaching for gene silencing via targeted DNA methylation. There is no written description of a chimeric protein which comprises a DNA binding sequence that specifically targets the promoter of an endogenous gene which is associated with cancer.

Applicant argues that one of ordinary skill in the art would be able to make the invention given the disclosure in the instant application and the teachings in the prior art. Applicant further argues that whether a chimeric protein is chosen that targets genes associated with cancer, AIDS, a central nervous system disorder, a blood disorder, a metabolic disorder, a cardiovascular disorder, an autoimmune disorder or an inflammatory disorder is irrelevant to whether applicant's invention is described. Applicant asserts that one of skill in the art would have known of many promoter sequences of genes known to be involved in cancer, would have known various DNA binding proteins which were known to specifically bind to specific DNA sequences of differing cancer types and would have known how to recognize a methylation site in a promoter sequence associated with cancer. This is not persuasive. The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for the chimeric proteins of the elected invention. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the *invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

As there is no disclosure of the chimeric proteins of the elected invention or of polynucleotides encoding said chimeric proteins, the skilled artisan cannot envision the detailed chemical structure of the encompassed chimeric proteins or polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The

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protein and/or polynucleotide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that applicant was in possession of the chimeric proteins of the elected invention or polynucleotides encoding said proteins, at the time the application was filed. Thus it is concluded that the written description provision of 35 U.S.C. §112, first paragraph, is not satisfied for the claimed chimeric proteins or polynucleotides of the elected invention. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record and the reasons below.

As stated in the previous Office action, the specification is not enabling for the claimed invention as the specification does not provide sufficient guidance for one of skill in the art to make and use the chimeric proteins of the elected invention as the specification does not provide any amino acid sequences for the chimeric proteins or polynucleotide sequences encoding the chimeric proteins which has the claim-designated properties of the elected invention. Thus, with regard to using the polynucleotide encoding the chimeric protein or the chimeric protein, itself, to methylate specific sites on a promoter, thereby inactivating the promoter and inhibiting expression of the promoter of an endogenous gene associated with cancer, the specification does not disclose any specific chimeric protein to be used in the method, nor does the specification disclose any specific polynucleotide which encodes the chimeric protein to be used in the claimed methods.

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Furthermore, the state of the art at the time of filing indicates that providing chimeric proteins with the claim-designated activities is neither routine nor predictable. For example, with regard to structure and function of methyltransferases, Bestor *et al.* (Curr. Op. Cell Biol., 6:380-389, 1994) state on page 384, left column, last paragraph:

“Just as important as recognizing a specific site is selecting the right cytosine to be methylated. Evidence suggests this selection is made primarily by the DNA-recognition domain, but it is still uncertain whether different DNA-recognition domains employ a common strategy. Many of these uncertainties could be resolved through acquisition of additional structures.”

With regard to the role of DNA methylation in carcinogenesis, Li *et al.* (Cell, 69:915-926, 1992) teach on page 923, right column, first full paragraph, that

“DNA methylation has been hypothesized to be involved in numerous processes, which include X inactivation, genomic imprinting, virus latency, carcinogenesis, aging, and the regulation of tissue-specific gene expression during development. The mutant ES cells and animals described here make possible rigorous tests of these hypotheses.”

Thus, while it is hypothesized that DNA methylation is involved in numerous processes, including carcinogenesis, the hypotheses remain to be tested.

Given the limited guidance in the specification as to which specific endogenous promoter sequence to target such that methylation of specific cytosines occurs which results in inhibition of expression of the associated gene, and given the teachings in the art with respect to the hypothesized function of DNA methylation in carcinogenesis and the importance of specific DNA-protein interactions which are required for targeted methylation, it would require undue experimentation for one of skill in the art to make and use the invention as claimed.

Applicant's arguments filed 1/16/01 have been fully considered but they are not persuasive.

It is argued that one of skill in the art, provided with guidance from the specification on page 29, line 33 through page 30, line 11 and Example 3 on page 44 could readily make chimeric proteins within the scope of applicant's claims and test which would work and which would not require undue experimentation. Applicant asserts that the specification teaches the construction

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of a chimeric protein which contains a zinc three-finger DNA binding component and a DNA methyltransferase protein with attenuated DNA binding activity which methylates a specific target promoter sequence. Applicant directs the examiner's attention to the specific and detailed methods for selection of zinc finger proteins that bind to predetermined sequences in the HIV-1 5' LTR and argues that given this exemplification and the directions for the design and selection of zinc finger-DNA methyltransferase chimeras on page 44, line 28 through page 45, line 9, Example, 1 and Figure 9 (see page 18 of applicant's Response). These arguments are not persuasive. As indicated by applicant, the methods are for selection of zinc finger proteins that bind to predetermined sequences in the HIV-1 5' LTR, not for methods for selection of zinc finger proteins that bind to any part of the sequence of an endogenous promoter in which the gene is associated with cancer. The disclosure on pages 44-45 are directed to the making of chimeras that methylate critical CpG sites in the HIV 5' LTR. Pages 44-45 do not disclose making chimeras that methylate critical CpG sites of promoters associated with cancer genes. Which sites are critical CpG sites in which promoters? With regard to Example 1, this example is not directed to the elected invention. However, with respect to Example 1, on page 40, lines 10-13, it should be noted that the specification discloses, with respect to obtain a methyltransferase with the claim-designated attenuated activity that "It cannot be predicted as to which mutations might give the desired reduction in affinity for DNA, so random mutations are introduced and selection is applied to obtain mutants of the desired character." In this regard, and with respect to the elected invention, the specification does not disclose the requisite desired reduction in affinity for an endogenous promoter which is associated with cancer, or what the structural characteristics of such mutants would be.

Applicant relies on the teachings in the references of Exhibit P as examples of known DNA sequences for which DNA-binding proteins are known to bind (see page 19 of applicant's Response). As discussed under the written description rejection, these references are directed to binding proteins which bind to intronic sequences, not promoter sequences, and these references

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do not teach binding proteins which will bind to endogenous promoters associated with cancer genes at regions in which methylation by the methyltransferase portion of the chimera can occur such that expression of the gene is inhibited.

Applicant also relies on Exhibit O which applicant asserts discloses sequences of target genes to which specific DNA-binding proteins bind (see page 20 of applicant's Response). The references of Exhibit O are GenBank accession numbers associated with osteopontin sequences from a number of species. As previously discussed, 10 of the 12 GenBank entries do not teach promoter sequences for osteopontin. The other 2 entries, which depict promoter sequences of the osteopontin genes from the pig and the chicken, do not provide information as to which promoter sequence to which the "specific DNA-bind proteins bind", nor is there information with respect to critical methylation sites. Applicant also relies on the disclosure in the specification with regard to identification of CpG sites in the HIV-1 5' LTR, and the construction and selection of a zinc-finger which will bind to the appropriate site on the HIV-1 5' LTR. As stated above, the HIV-1 5' LTR is not an endogenous promoter associated with a cancer gene.

With regard to endocytosis of the protein, applicant argues that one of skill in the art, given the disclosure in the specification, would be able to construct a chimeric protein which would be capable of binding to a predetermined target promoter sequence with a methylation site to inhibit gene expression as exemplified in Figure 1 which depicts inactivation of 5' LTR of HIV-1 by targeted cytosine methylation (see page 20 of applicant's Response). This is not persuasive as the specification does not disclose a chimeric protein which is capable of binding to a predetermined target promoter sequence, wherein the promoter sequence is endogenous and associated with cancer, and which comprises a methylation site, which when methylated by the methyltransferase, is no longer expressed. As the specification does not provide sufficient guidance for making the chimeric protein, methods of using the chimeric protein for inhibiting gene expression in vitro or in vivo are not enabled. In addition, with respect to *in vivo* use of the chimeric protein, the specification does not provide sufficient guidance for the skilled artisan to

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administer such a protein such that the protein is targeted to the correct cell, is endocytosed, is translocated into the nucleus, and which binds to the correct promoter such that the expression of the appropriate gene is inhibited.

With respect to gene therapy, it is argued that all that is needed to practice is disclosed (applicant refers to page 22, line 6 through page 23, line 4, and page 22, lines 13-21 of the specification), the rest is known to those of skill in the art (see page 20 of applicant's Response). This argument is not persuasive. As indicated in the previous Office action, gene therapy is not a routine or predictable art. There is no objective evidence of record that a vector comprising a polynucleotide encoding the non-disclosed chimeric protein can be administered *in vivo* such that the vector is targeted to the appropriate cells/tissues, is expressed at an appropriate level, and is capable of inhibiting the expression of a specific gene via methylation of a specific endogenous promoter sequence of a gene associated with cancer.

For the reasons of record and the reasons set forth above, the rejection is maintained.

Claims 1, 4, 6-12, 15, 16, 24-28, 30-33, and 42-46 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 are rendered vague and indefinite by the phrase "attenuated DNA binding activity" as it is unclear as to what the "attenuated DNA binding activity" is relative, i.e., a naturally occurring DNA methyltransferase? It is suggested that applicant include in the claim "relative to said naturally occurring DNA methyltransferase" or similar language which is supported by the specification.

No claims are allowed.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

  
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